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(54) Title: COMBINATION OF ZD6474, AN INHIBITOR OF THE VASCULAR ENDOTHELIAL GROWTH FACTOR RECEPTOR, WITH RADIOTHERAPY IN THE TREATMENT OF CANCER

(57) Abstract: The present invention relates to a method for the production of an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal such as a human, particularly a method for the treatment of a cancer, particularly a cancer involving a solid tumour, which comprises the administration of ZD6474 in combination with ionising radiation; and to the use of ZD6474 in the manufacture of a medicament for use in the production of an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal such as a human which is being treated with ionising radiation.

WO 2004/014383 A1

COMBINATION OF ZD6474, AN INHIBITOR OF THE VASCULAR ENDOTHELIAL GROWTH FACTOR  
RECEPTOR, WITH RADIOTHERAPY IN THE TREATMENT OF CANCER

The present invention relates to a method for the production of an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal such as a human, particularly a method for the treatment of a cancer, particularly a cancer involving a solid  
5 tumour, which comprises the administration of ZD6474 in combination with ionising radiation; and to the use of ZD6474 in the manufacture of a medicament for use in the production of an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal such as a human which is being treated with ionising radiation.

Normal angiogenesis plays an important role in a variety of processes including  
10 embryonic development, wound healing and several components of female reproductive function. Undesirable or pathological angiogenesis has been associated with disease states including diabetic retinopathy, psoriasis, cancer, rheumatoid arthritis, atheroma, Kaposi's sarcoma and haemangioma (Fan et al, 1995, Trends Pharmacol. Sci. 16: 57-66; Folkman, 1995, Nature Medicine 1: 27-31). Alteration of vascular permeability is thought to play a role in both  
15 normal and pathological physiological processes (Cullinan-Bove et al, 1993, Endocrinology 133: 829-837; Senger et al, 1993, Cancer and Metastasis Reviews, 12: 303-324). Several polypeptides with *in vitro* endothelial cell growth promoting activity have been identified including, acidic and basic fibroblast growth factors (aFGF & bFGF) and vascular endothelial growth factor (VEGF). By virtue of the restricted expression of its receptors, the growth factor  
20 activity of VEGF, in contrast to that of the FGFs, is relatively specific towards endothelial cells. Recent evidence indicates that VEGF is an important stimulator of both normal and pathological angiogenesis (Jakeman et al, 1993, Endocrinology, 133: 848-859; Kolch et al, 1995, Breast Cancer Research and Treatment, 36:139-155) and vascular permeability (Connolly et al, 1989, J. Biol. Chem. 264: 20017-20024). Antagonism of VEGF action by sequestration of VEGF with  
25 antibody can result in inhibition of tumour growth (Kim et al, 1993, Nature 362: 841-844).

Receptor tyrosine kinases (RTKs) are important in the transmission of biochemical signals across the plasma membrane of cells. These transmembrane molecules characteristically consist of an extracellular ligand-binding domain connected through a segment in the plasma membrane to an intracellular tyrosine kinase domain. Binding of ligand to the receptor results in  
30 stimulation of the receptor-associated tyrosine kinase activity which leads to phosphorylation of tyrosine residues on both the receptor and other intracellular molecules. These changes in tyrosine phosphorylation initiate a signalling cascade leading to a variety of cellular responses.

To date, at least nineteen distinct RTK subfamilies, defined by amino acid sequence homology, have been identified. One of these subfamilies is presently comprised by the *fms*-like tyrosine kinase receptor Flt-1, the kinase insert domain-containing receptor, KDR (also referred to as Flk-1), and another *fms*-like tyrosine kinase receptor, Flt-4. Two of these related RTKs, Flt-1  
5 and KDR, have been shown to bind VEGF with high affinity (De Vries et al, 1992, *Science* 255: 989-991; Terman et al, 1992, *Biochem. Biophys. Res. Comm.* 1992, 187: 1579-1586). Binding of VEGF to these receptors expressed in heterologous cells has been associated with changes in the tyrosine phosphorylation status of cellular proteins and calcium fluxes.

VEGF is a key stimulus for vasculogenesis and angiogenesis. This cytokine induces a  
10 vascular sprouting phenotype by inducing endothelial cell proliferation, protease expression and migration, and subsequent organisation of cells to form a capillary tube (Keck, P.J., Hauser, S.D., Krivi, G., Sanzo, K., Warren, T., Feder, J., and Connolly, D.T., *Science* (Washington DC), 246: 1309-1312, 1989; Lamoreaux, W.J., Fitzgerald, M.E., Reiner, A., Hasty, K.A., and Charles, S.T., *Microvasc. Res.*, 55: 29-42, 1998; Pepper, M.S., Montesano,  
15 R., Mandroita, S.J., Orci, L. and Vassalli, J.D., *Enzyme Protein*, 49: 138-162, 1996.). In addition, VEGF induces significant vascular permeability (Dvorak, H.F., Detmar, M., Claffey, K.P., Nagy, J.A., van de Water, L., and Senger, D.R., (*Int. Arch. Allergy Immunol.*, 107: 233-235, 1995; Bates, D.O., Heald, R.I., Curry, F.E. and Williams, B. *J. Physiol. (Lond.)*, 533: 263-272, 2001), promoting formation of a hyper-permeable, immature vascular network which  
20 is characteristic of pathological angiogenesis.

It has been shown that activation of KDR alone is sufficient to promote all of the major phenotypic responses to VEGF, including endothelial cell proliferation, migration, and survival, and the induction of vascular permeability (Meyer, M., Clauss, M., Lepple-Wienhues, A., Waltenberger, J., Augustin, H.G., Ziche, M., Lanz, C., Büttner, M., Rziha, H-J., and Dehio,  
25 C., *EMBO J.*, 18: 363-374, 1999; Zeng, H., Sanyal, S. and Mukhopadhyay, D., *J. Biol. Chem.*, 276: 32714-32719, 2001; Gille, H., Kowalski, J., Li, B., LeCouter, J., Moffat, B, Zioncheck, T.F., Pelletier, N. and Ferrara, N., *J. Biol. Chem.*, 276: 3222-3230, 2001).

The use of ionising radiation and a VEGF antibody in a number of mouse xenograft models has been described (Gorski et al, 1999, *Cancer Res.* 59, 3374-3378 and International  
30 Patent Application Publication No. WO 00/61186).

The use of ionising radiation and a soluble VEGF receptor (soluble Flk-1) and the use of ionising radiation and a KDR inhibitor, SU5416, in a mouse glioma xenograft model have been

described (Geng et al, 2001, Cancer Res. 61, 2413-2419).

Quinazoline derivatives which are inhibitors of VEGF receptor tyrosine kinase are described in International Patent Applications Publication Nos. WO 98/13354 and WO 01/32651. In WO 98/13354 and WO 01/32651 compounds are described which possess activity  
5 against VEGF receptor tyrosine kinase whilst possessing some activity against EGF receptor tyrosine kinase. The compound of the present invention, ZD6474, falls within the broad general disclosure of WO 98/13354 and is exemplified in WO 01/32651.

In WO 01/32651 it is stated that compounds of that invention:

“may be applied as a sole therapy or may involve, in addition to a compound of the invention,  
10 one or more other substances and/or treatments. Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate administration of the individual components of the treatment.”

WO 01/32651 then goes on to describe examples of such conjoint treatment including surgery, radiotherapy and various types of chemotherapeutic agent. Nowhere in WO 01/32651  
15 does it state that use of any compound of the invention therein with other treatments will produce surprisingly beneficial effects.

Unexpectedly and surprisingly we have now found that the particular compound ZD6474 used in combination with a particular selection of the combination therapies listed in WO 01/32651, namely with ionising radiation, produces significantly better effects than any  
20 one of ZD6474 and ionising radiation used alone.

According to one aspect of the present invention ZD6474 used in combination with ionising radiation produces significantly better anti-cancer effects than any one of ZD6474 and ionising radiation used alone.

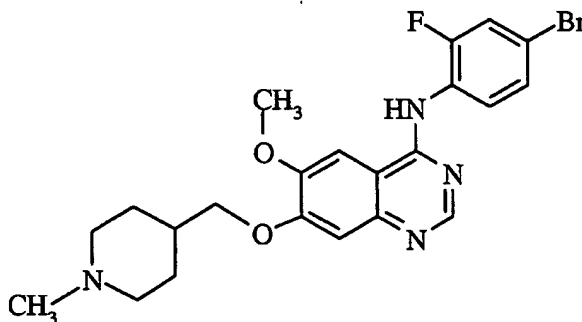
According to one aspect of the present invention ZD6474 used in combination with  
25 ionising radiation produces significantly better effects against a solid tumour than any one of ZD6474 and ionising radiation used alone.

Anti-cancer effects of a method of treatment of the present invention include, but are not limited to, anti-tumour effects, the response rate, the time to disease progression and the survival rate. Anti-tumour effects of a method of treatment of the present invention include,  
30 but are not limited to, inhibition of tumour growth, tumour growth delay, regression of tumour, shrinkage of tumour, increased time to regrowth of tumour on cessation of treatment, slowing of disease progression. It is expected that when a method of treatment of the present

invention is administered to a warm-blooded animal such as a human, in need of treatment for cancer, with or without a solid tumour, said method of treatment will produce an effect, as measured by, for example, one or more of: the extent of the anti-tumour effect, the response rate, the time to disease progression and the survival rate.

- 5 According to the present invention there is provided a method for the production of an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal such as a human, which comprises administering to said animal an effective amount of 4-(4-bromo-2-fluoroanilino)-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline, also known as ZD6474:

10



ZD6474

- or a pharmaceutically acceptable salt thereof, before, after or simultaneously with an effective  
15 amount of ionising radiation.

According to a further aspect of the present invention there is provided a method for the treatment of a cancer in a warm-blooded animal such as a human, which comprises administering to said animal an effective amount of ZD6474 or a pharmaceutically acceptable salt thereof, before, after or simultaneously with an effective amount of ionising radiation.

- 20 According to a further aspect of the present invention there is provided a method for the treatment of a cancer involving a solid tumour in a warm-blooded animal such as a human, which comprises administering to said animal an effective amount of ZD6474 or a pharmaceutically acceptable salt thereof, before, after or simultaneously with an effective amount of ionising radiation.

- 25 According to a further aspect of the present invention there is provided the use of ZD6474 or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for

use in the production of an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal such as a human which is being treated with ionising radiation.

According to a further aspect of the present invention there is provided the use of ZD6474 or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for  
5 use in the production of an anti-cancer effect in a warm-blooded animal such as a human which is being treated with ionising radiation.

According to a further aspect of the present invention there is provided the use of ZD6474 or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in the production of an anti-tumour effect in a warm-blooded animal such as a human  
10 which is being treated with ionising radiation.

A warm-blooded animal such as a human which is being treated with ionising radiation means a warm-blooded animal such as a human which is treated with ionising radiation before, after or at the same time as the administration of a medicament comprising ZD6474. For example said ionising radiation may be given to said warm-blooded animal such as a human  
15 within the period of a week before to a week after the administration of a medicament comprising ZD6474. According to one aspect of the present invention ZD6474 is administered to a warm-blooded animal after the animal has been treated with ionising radiation. The warm-blooded animal may experience the effect of each of ZD6474 and ionising radiation simultaneously.

20 As stated above the combination treatments of the present invention as defined herein are of interest for their antiangiogenic and/or vascular permeability effects. Such combination treatments of the invention are expected to be useful in the prophylaxis and treatment of a wide range of disease states where inappropriate angiogenesis occurs including cancer and Kaposi's sarcoma. Cancer may affect any tissue and includes leukaemia, multiple myeloma and  
25 lymphoma. In particular such combination treatments of the invention are expected to slow advantageously the growth of primary and recurrent solid tumours of, for example, the colon, breast, prostate, lungs and skin. More especially combination treatments of the present invention are expected to slow advantageously the growth of tumours in lung cancer, particularly non-small cell lung cancer (NSCLC). More particularly such combination  
30 treatments of the invention are expected to inhibit any form of cancer associated with VEGF including leukaemia, multiple myeloma and lymphoma and also, for example, to inhibit the growth of those primary and recurrent solid tumours which are associated with VEGF,

especially those tumours which are significantly dependent on VEGF for their growth and spread, including for example, certain tumours of the colon, breast, prostate, lung, vulva and skin, particularly NSCLC.

In another aspect of the present invention ZD6474 and ionising radiation are expected to inhibit the growth of those primary and recurrent solid tumours which are associated with EGF especially those tumours which are significantly dependent on EGF for their growth and spread.

In another aspect of the present invention ZD6474 and ionising radiation are expected to inhibit the growth of those primary and recurrent solid tumours which are associated with both VEGF and EGF especially those tumours which are significantly dependent on VEGF and EGF for their growth and spread.

According to another aspect of the present invention the effect of a method of treatment of the present invention is expected to be at least equivalent to the addition of the effects of each of the components of said treatment used alone, that is, of each of ZD6474 and ionising radiation, used alone.

According to another aspect of the present invention the effect of a method of treatment of the present invention is expected to be greater than the addition of the effects of each of the components of said treatment used alone, that is, of each of ZD6474 and ionising radiation, used alone.

According to another aspect of the present invention the effect of a method of treatment of the present invention is expected to be a synergistic effect.

It should also be appreciated that according to the present invention a combination treatment is defined as affording a synergistic effect if the effect is therapeutically superior, as measured by, for example, the extent of the response, the response rate, the time to disease progression or the survival period, to that achievable on dosing one or other of the components of the combination treatment at its conventional dose. For example, the effect of the combination treatment is synergistic if the effect is therapeutically superior to the effect achievable with ZD6474 or ionising radiation alone. Further, the effect of the combination treatment is synergistic if a beneficial effect is obtained in a group of patients that does not respond (or responds poorly) to ZD6474 or ionising radiation alone. In addition, the effect of the combination treatment is defined as affording a synergistic effect if one of the components is dosed at its conventional dose and the other component is dosed at a reduced dose and the



therapeutic effect, as measured by, for example, the extent of the response, the response rate, the time to disease progression or the survival period, is equivalent to that achievable on dosing conventional amounts of the components of the combination treatment. In particular, synergy is deemed to be present if the conventional dose of ZD6474 or ionising radiation may  
5 be reduced without detriment to one or more of the extent of the response, the response rate, the time to disease progression and survival data, in particular without detriment to the duration of the response, but with fewer and/or less troublesome side-effects than those that occur when conventional doses of each component are used.

A combination method of treatment of the present invention as defined herein may be  
10 achieved by way of the simultaneous, sequential or separate administration of the individual components of said treatment. A combination treatment as defined herein may be applied as a sole therapy or may involve surgery, in addition to a combination method of treatment of the invention. Surgery may comprise the step of partial or complete tumour resection, prior to, during or after the administration of the combination treatment with ZD6474 described herein.

15 The compositions described herein may be in a form suitable for oral administration, for example as a tablet or capsule, for nasal administration or administration by inhalation, for example as a powder or solution, for parenteral injection (including intravenous, subcutaneous, intramuscular, intravascular or infusion) for example as a sterile solution, suspension or emulsion, for topical administration for example as an ointment or cream, for rectal  
20 administration for example as a suppository or the route of administration may be by direct injection into the tumour or by regional delivery or by local delivery. In other embodiments of the present invention the ZD6474 of the combination treatment may be delivered endoscopically, intratracheally, intralesionally, percutaneously, intravenously, subcutaneously, intraperitoneally or intratumourally. Preferably ZD6474 is administered orally. In general the  
25 compositions described herein may be prepared in a conventional manner using conventional excipients. The compositions of the present invention are advantageously presented in unit dosage form.

ZD6474 will normally be administered to a warm-blooded animal at a unit dose within the range 10-500mg per square metre body area of the animal, for example approximately 0.3-  
30 15mg/kg in a human. A unit dose in the range, for example, 0.3-15mg/kg, preferably 0.5-5mg/kg is envisaged and this is normally a therapeutically-effective dose. A unit dosage

form such as a tablet or capsule will usually contain, for example 25-500mg of active ingredient. Preferably a daily dose in the range of 0.5-5mg/kg is employed.

In particular embodiments of the present invention the ionising radiation employed may be X-radiation,  $\gamma$ -radiation or  $\beta$ -radiation.

5       The dosages of ionising radiation will be those known for use in clinical radiotherapy. The radiation therapy used will include for example the use of  $\gamma$ -rays, X-rays, and/or the directed delivery of radiation from radioisotopes. Other forms of DNA damaging factors are also included in the present invention such as microwaves and UV-irradiation. It is most likely that all of these factors effect a broad range of damage on DNA, on the precursors of DNA, on  
10 the replication and repair of DNA and on the assembly and maintenance of chromosomes. For example X-rays may be dosed in daily doses of 1.8-2.0Gy, 5 days a week for 5-6 weeks. Normally a total fractionated dose will lie in the range 45-60Gy. Single larger doses, for example 5-10Gy may be administered as part of a course of radiotherapy. Single doses may be administered intraoperatively. Hyperfractionated radiotherapy may be used whereby small  
15 doses of X-rays are administered regularly over a period of time, for example 0.1Gy per hour over a number of days. Dosage ranges for radioisotopes vary widely, and depend on the half-life of the isotope, the strength and type of radiation emitted, and on the uptake by cells.

As stated above the size of the dose of each therapy which is required for the therapeutic or prophylactic treatment of a particular disease state will necessarily be varied  
20 depending on the host treated, the route of administration and the severity of the illness being treated. Accordingly the optimum dosage may be determined by the practitioner who is treating any particular patient. For example, it may be necessary or desirable to reduce the above-mentioned doses of the components of the combination treatments in order to reduce toxicity.

25       The present invention relates to combinations of ionising radiation with ZD6474 or with a salt of ZD6474.

Salts for use in pharmaceutical compositions will be pharmaceutically acceptable salts, but other salts may be useful in the production of ZD6474 and its pharmaceutically acceptable salts. Such salts may be formed with an inorganic or organic base which affords a  
30 pharmaceutically acceptable cation. Such salts with inorganic or organic bases include for example an alkali metal salt, such as a sodium or potassium salt, an alkaline earth metal salt such as a calcium or magnesium salt, an ammonium salt or for example a salt with

methylamine, dimethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine.

ZD6474 may be made, for example, according to any of the following processes illustrated by examples (a) –(c) in which, unless otherwise stated:-

- 5 (i) evaporations were carried out by rotary evaporation in vacuo and work-up procedures were carried out after removal of residual solids such as drying agents by filtration;
- (ii) operations were carried out at ambient temperature, that is in the range 18-25°C and under an atmosphere of an inert gas such as argon;
- (iii) column chromatography (by the flash procedure) and medium pressure liquid  
10 chromatography (MPLC) were performed on Merck Kieselgel silica (Art. 9385) or Merck Lichroprep RP-18 (Art. 9303) reversed-phase silica obtained from E. Merck, Darmstadt, Germany;
- (iv) yields are given for illustration only and are not necessarily the maximum attainable;
- (v) melting points are uncorrected and were determined using a Mettler SP62 automatic  
15 melting point apparatus, an oil-bath apparatus or a Koffler hot plate apparatus.
- (vi) the structures of the end-products of the formula I were confirmed by nuclear (generally proton) magnetic resonance (NMR) and mass spectral techniques; proton magnetic resonance chemical shift values were measured on the delta scale and peak multiplicities are shown as follows: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad; q, quartet; NMR  
20 spectra were run on a 400MHz machine at 24°C.
- (vii) intermediates were not generally fully characterised and purity was assessed by thin layer chromatography (TLC), high-performance liquid chromatography (HPLC), infra-red (IR) or NMR analysis;
- (viii) the following abbreviations have been used:-

25

DMF N,N-dimethylformamide

DMSO dimethylsulphoxide

THF tetrahydrofuran

TFA trifluoroacetic acid

30

NMP 1-methyl-2-pyrrolidinone.]

Process (a)

- A solution of 37% aqueous formaldehyde (50 $\mu$ l, 0.6mmol) followed by sodium cyanoborohydride (23mg, 0.36mmol) were added to a solution of 4-(4-bromo-2-fluoroanilino)-6-methoxy-7-(piperidin-4-ylmethoxy)quinazoline (139mg, 0.3mmol), in a mixture of
- 5 THF/methanol (1.4ml/1.4ml). After stirring for 1 hour at ambient temperature, water was added and the volatiles were removed under vacuum. The residue was triturated with water, filtered, washed with water, and dried under vacuum. The solid was purified by chromatography on neutral alumina eluting with methylene chloride followed by methylene chloride/ethyl acetate (1/1) followed by methylene chloride/ethyl acetate/methanol (50/45/5).
- 10 The fractions containing the expected product were evaporated under vacuum. The resulting white solid was dissolved in methylene chloride/methanol (3ml/3ml) and 3N hydrogen chloride in ether (0.5ml) was added. The volatiles were removed under vacuum. The solid was triturated with ether, filtered, washed with ether and dried under vacuum to give 4-(4-bromo-2-fluoroanilino)-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline hydrochloride
- 15 (120mg, 69%).

MS - ESI: 475-477 [MH]<sup>+</sup>

The NMR spectrum of the protonated form of 4-(4-bromo-2-fluoroanilino)-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline hydrochloride shows the presence of 2 forms A and B in a ratio A:B of approximately 9:1.

- 20 <sup>1</sup>H NMR Spectrum: (DMSO-d<sub>6</sub>; CF<sub>3</sub>COOD) 1.55-1.7 (m, form A 2H) ; 1.85-2.0 (m, form B 4H) ; 2.03 (d, form A 2H) ; 2.08-2.14 (br s, form A 1H) ; 2.31-2.38 (br s, form B 1H) ; 2.79 (s, form A 3H) ; 2.82 (s, form B 3H) ; 3.03 (t, form A 2H) ; 3.21 (br s, form B 2H) ; 3.30 (br s, form B 2H) ; 3.52 (d, form A 2H) ; 4.02 (s, 3H) ; 4.12 (d, form A 2H) ; 4.30 (d, form B 2H) ; 7.41 (s, 1H) ; 7.5-7.65 (m, 2H) ; 7.81 (d, 1H) ; 8.20 (s, 1H) ; 8.88 (s, 1H)
- 25 Elemental analysis: Found C 46.0 H 5.2 N 9.6  
 C<sub>22</sub>H<sub>24</sub>N<sub>4</sub>O<sub>2</sub>BrF 0.3H<sub>2</sub>O 2.65HCl Requires C 45.8 H 4.8 N 9.7%

The starting material was prepared as follows:

- A solution of 7-benzyloxy-4-chloro-6-methoxyquinazoline hydrochloride (8.35g, 27.8mmol), (prepared, for example, as described in WO 97/22596, Example 1), and 4-bromo-
- 30 2-fluoroaniline (5.65g, 29.7mmol) in 2-propanol (200ml) was heated at reflux for 4 hours. The resulting precipitate was collected by filtration, washed with 2-propanol and then ether and

dried under vacuum to give 7-benzyloxy-4-(4-bromo-2-fluoroanilino)-6-methoxyquinazoline hydrochloride (9.46g, 78%).

<sup>1</sup>H NMR Spectrum: (DMSO-d<sub>6</sub>; CD<sub>3</sub>COOD) 4.0(s, 3H); 5.37(s, 2H); 7.35-7.5(m, 4H); 7.52-7.62(m, 4H); 7.8(d, 1H); 8.14(9s, 1H); 8.79(s, 1H)

5 MS - ESI: 456 [MH]<sup>+</sup>

Elemental analysis:	Found	C 54.0	H 3.7	N 8.7
C <sub>22</sub> H <sub>17</sub> N <sub>3</sub> O <sub>2</sub> BrF 0.9HCl	Requires	C 54.2	H 3.7	N 8.6%

A solution of 7-benzyloxy-4-(4-bromo-2-fluoroanilino)-6-methoxyquinazoline hydrochloride (9.4g, 19.1mmol) in TFA (90ml) was heated at reflux for 50 minutes. The mixture was allowed to cool and was poured on to ice. The resulting precipitate was collected by filtration and dissolved in methanol (70ml). The solution was adjusted to pH9-10 with concentrated aqueous ammonia solution. The mixture was concentrated to half initial volume by evaporation. The resulting precipitate was collected by filtration, washed with water and then ether, and dried under vacuum to give 4-(4-bromo-2-fluoroanilino)-7-hydroxy-6-methoxyquinazoline (5.66g, 82%).

<sup>1</sup>H NMR Spectrum: (DMSO-d<sub>6</sub>; CD<sub>3</sub>COOD) 3.95(s, 3H); 7.09(s, 1H); 7.48(s, 1H); 7.54(t, 1H); 7.64(d, 1H); 7.79(s, 1H); 8.31(s, 1H)

MS - ESI: 366 [MH]<sup>+</sup>

Elemental analysis:	Found	C 49.5	H 3.1	N 11.3
20 C <sub>15</sub> H <sub>11</sub> N <sub>3</sub> O <sub>2</sub> BrF	Requires	C 49.5	H 3.0	N 11.5%

While maintaining the temperature in the range 0-5°C, a solution of di-*tert*-butyl dicarbonate (41.7g, 0.19mol) in ethyl acetate (75ml) was added in portions to a solution of ethyl 4-piperidinecarboxylate (30g, 0.19mol) in ethyl acetate (150ml) cooled at 5°C. After stirring for 48 hours at ambient temperature, the mixture was poured onto water (300ml). The organic layer was separated, washed successively with water (200ml), 0.1N aqueous hydrochloric acid (200ml), saturated sodium hydrogen carbonate (200ml) and brine (200ml), dried (MgSO<sub>4</sub>) and evaporated to give ethyl 4-(1-(*tert*-butoxycarbonyl)piperidine)carboxylate (48g, 98%).

<sup>1</sup>H NMR Spectrum: (CDCl<sub>3</sub>) 1.25(t, 3H); 1.45(s, 9H); 1.55-1.70(m, 2H); 1.8-2.0(d, 2H); 2.35-2.5(m, 1H); 2.7-2.95(t, 2H); 3.9-4.1(br s, 2H); 4.15 (q, 2H)

A solution of 1M lithium aluminium hydride in THF (133ml, 0.133mol) was added in portions to a solution of ethyl 4-(1-(*tert*-butoxycarbonyl)piperidine)carboxylate (48g, 0.19mol)

in dry THF (180ml) cooled at 0°C. After stirring at 0°C for 2 hours, water (30ml) was added followed by 2N sodium hydroxide (10ml). The precipitate was removed by filtration through diatomaceous earth and washed with ethyl acetate. The filtrate was washed with water, brine, dried (MgSO<sub>4</sub>) and evaporated to give 1-(*tert*-butoxycarbonyl)-4-hydroxymethylpiperidine

5 (36.3g, 89%).

MS (EI): 215 [M.]<sup>+</sup>

<sup>1</sup>H NMR Spectrum: (CDCl<sub>3</sub>) 1.05-1.2(m, 2H); 1.35-1.55(m, 10H); 1.6-1.8(m, 2H); 2.6-2.8(t, 2H); 3.4-3.6(t, 2H); 4.0-4.2(br s, 2H)

1,4-Diazabicyclo[2.2.2]octane (42.4g, 0.378mol) was added to a solution of 1-(*tert*-  
10 butoxycarbonyl)-4-hydroxymethylpiperidine (52.5g, 0.244mol) in *tert*-butyl methyl ether (525ml). After stirring for 15 minutes at ambient temperature, the mixture was cooled to 5°C and a solution of toluene sulphonyl chloride (62.8g, 0.33mmol) in *tert*-butyl methyl ether (525ml) was added in portions over 2 hours while maintaining the temperature at 0°C. After stirring for 1 hour at ambient temperature, petroleum ether (1l) was added. The precipitate  
15 was removed by filtration. The filtrate was evaporated to give a solid. The solid was dissolved in ether and washed successively with 0.5N aqueous hydrochloric acid (2x500ml), water, saturated sodium hydrogen carbonate and brine, dried (MgSO<sub>4</sub>) and evaporated to give 1-(*tert*-butoxycarbonyl)-4-(4-methylphenylsulphonyloxymethyl)piperidine (76.7g, 85%).

MS (ESI): 392 [MNa]<sup>+</sup>

20 <sup>1</sup>H NMR Spectrum: (CDCl<sub>3</sub>) 1.0-1.2(m, 2H); 1.45(s, 9H); 1.65(d, 2H); 1.75-1.9(m, 2H); 2.45(s, 3H); 2.55-2.75(m, 2H); 3.85(d, 1H); 4.0-4.2(br s, 2H); 7.35(d, 2H); 7.8(d, 2H)

Potassium carbonate (414mg, 3mmol) was added to a suspension of 4-(4-bromo-2-fluoroanilino)-7-hydroxy-6-methoxyquinazoline (546mg, 1.5mmol) in DMF (5ml). After stirring for 10 minutes at ambient temperature, 1-(*tert*-butoxycarbonyl)-4-(4-methylphenylsulphonyloxymethyl)piperidine (636mg, 1.72mmol) was added and the mixture  
25 was heated at 95°C for 2 hours. After cooling, the mixture was poured onto cooled water (20ml). The precipitate was collected by filtration, washed with water, and dried under vacuum to give 4-(4-bromo-2-fluoroanilino)-7-(1-(*tert*-butoxycarbonyl)piperidin-4-ylmethoxy)-6-methoxyquinazoline (665mg, 79%).

30 MS - ESI: 561-563 [MH]<sup>+</sup>

<sup>1</sup>H NMR Spectrum: (DMSO-d<sub>6</sub>) 1.15-1.3 (m, 2H), 1.46 (s, 9H), 1.8 (d, 2H), 2.0-2.1 (m, 1H), 2.65-2.9 (m, 2H), 3.95 (s, 3H), 4.02 (br s, 2H), 4.05 (d, 2H), 7.2 (s, 1H), 7.48 (d, 1H), 7.55 (t, 1H), 7.65 (d, 1H), 7.8 (s, 1H), 8.35 (s, 1H), 9.55 (br s, 1H)

TFA (3ml) was added to a suspension of 4-(4-bromo-2-fluoroanilino)-7-(1-(*tert*-butoxycarbonyl)piperidin-4-ylmethoxy)-6-methoxyquinazoline (673mg, 1.2mmol) in methylene chloride (10ml). After stirring for 1 hour at ambient temperature, the volatiles were removed under vacuum. The residue was triturated with a mixture of water/ether. The organic layer was separated. The aqueous layer was washed again with ether. The aqueous layer was adjusted to pH10 with 2N aqueous sodium hydroxide. The aqueous layer was extracted with methylene chloride. The organic layer was dried (MgSO<sub>4</sub>) and the solvent was removed under vacuum. The solid was triturated with a mixture ether/petroleum ether (1/1), filtered, washed with ether and dried under vacuum to give 4-(4-bromo-2-fluoroanilino)-6-methoxy-7-(piperidin-4-ylmethoxy)quinazoline (390mg, 70.5%).

MS - ESI: 461-463 [MH]<sup>+</sup>

<sup>1</sup>H NMR Spectrum: (DMSO-d<sub>6</sub>) 1.13-1.3 (m, 2H), 1.75 (d, 2H), 1.87-2.0 (m, 1H), 2.5 (d, 2H), 3.0 (d, 2H), 3.96 (s, 3H), 3.98 (d, 2H), 7.2 (s, 1H), 7.5 (dd, 1H), 7.55 (t, 1H), 7.68 (dd, 1H), 7.80 (s, 1H), 8.36 (s, 1H), 9.55 (br s, 1H)

Elemental analysis:	Found	C 54.5	H 4.9	N 12.1
C <sub>21</sub> H <sub>22</sub> N <sub>4</sub> O <sub>2</sub> BrF	Requires	C 54.7	H 4.8	N 12.1%

## 20 Process (b)

37% Aqueous formaldehyde (3.5ml, 42mmol) was added to a solution of 4-(4-bromo-2-fluoroanilino)-7-(1-(*tert*-butoxycarbonyl)piperidin-4-ylmethoxy)-6-methoxyquinazoline (3.49g, 6.22mmol), (prepared as described for the starting material in process (a) above), in formic acid (35ml). After heating at 95°C for 4 hours the volatiles were removed under vacuum. The residue was suspended in water and the mixture was adjusted to pH10.5 by slow addition of a solution of 2N sodium hydroxide. The suspension was extracted with ethyl acetate. The organic layer was washed with brine, dried MgSO<sub>4</sub> and evaporated to give 4-(4-bromo-2-fluoroanilino)-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline (2.61g, 88%).

MS - ESI: 475-477 [MH]<sup>+</sup>

<sup>1</sup>H NMR Spectrum: (DMSO-d<sub>6</sub>) 1.3-1.45 (m, 2H), 1.8 (d, 2H), 1.7-1.9 (m, 1H), 1.95 (t, 2H), 2.2 (s, 3H), 2.85 (d, 2H), 3.96 (s, 3H), 4.05 (d, 2H), 7.19 (s, 1H), 7.5 (d, 1H), 7.55 (t, 1H), 7.67 (d, 1H), 7.81 (s, 1H), 8.37 (s, 1H), 9.54 (s, 1H)

Elemental analysis: Found C 55.4 H 5.1 N 11.6

5 C<sub>22</sub>H<sub>24</sub>N<sub>4</sub>O<sub>2</sub>BrF Requires C 55.6 H 5.1 N 11.8%

#### Process (c)

A suspension of 4-chloro-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline (200mg, 0.62mmol) and 4-bromo-2-fluoroaniline (142mg, 0.74mmol) in isopropanol (3ml) containing 6N hydrogen chloride in isopropanol (110μl, 0.68ml) was heated at reflux for 1.5  
10 hours. After cooling, the precipitate was collected by filtration, washed with isopropanol followed by ether and dried under vacuum to give 4-(4-bromo-2-fluoroanilino)-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline hydrochloride (304mg, 90%).

Elemental analysis: Found C 47.9 H 4.9 N 10.0

C<sub>22</sub>H<sub>24</sub>N<sub>4</sub>O<sub>2</sub>BrF 0.5H<sub>2</sub>O 1.8HCl Requires C 48.2 H 5.0 N 10.1%

15 0.08 isopropanol

The NMR spectrum of the protonated form of 4-(4-bromo-2-fluoroanilino)-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline hydrochloride shows the presence of two forms A and B in a ratio A:B of approximately 9:1.

<sup>1</sup>H NMR Spectrum: (DMSO-d<sub>6</sub>) 1.6-1.78 (m, form A 2H); 1.81-1.93 (br s, form B 4H); 1.94-  
20 2.07 (d, form A 2H); 2.08-2.23 (br s, form A 1H); 2.29-2.37 (br s, form B 1H); 2.73 (d, form A 3H); 2.77 (d, form B 3H); 2.93-3.10 (q, form A 2H); 3.21 (br s, form B 2H); 3.27 (br s, form B 2H); 3.42-3.48 (d, form A 2H); 4.04 (s, 3H); 4.10 (d, form A 2H); 4.29 (d, form B 2H); 7.49 (s, 1H); 7.53-7.61 (m, 2H); 7.78 (d, 1H); 8.47 (s, 1H); 8.81 (s, 1H); 10.48 (br s, form A 1H); 10.79 (br s, form B 1H); 11.90 (br s, 1H)

25 For another NMR reading, some solid potassium carbonate was added into the DMSO solution of the 4-(4-bromo-2-fluoroanilino)-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline hydrochloride described above, in order to release the free base in the NMR tube. The NMR spectrum was then recorded again and showed only one form as described below:

30 <sup>1</sup>H NMR Spectrum: (DMSO-d<sub>6</sub>; solid potassium carbonate) 1.3-1.45 (m, 2H); 1.75 (d, 2H); 1.7-1.9(m, 1H); 1.89 (t, 2H); 2.18 (s, 3H); 2.8 (d, 2H); 3.98 (s, 3H); 4.0 (d, 2H); 7.2 (s, 1H); 7.48 (d, 1H); 7.55 (t, 1H); 7.68 (d, 1H); 7.8 (s, 1H); 8.35 (s, 1H); 9.75 (s, 1H)



A sample of 4-(4-bromo-2-fluoroanilino)-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline (free base) was generated from the 4-(4-bromo-2-fluoroanilino)-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline hydrochloride, (prepared as described above), as follows:

- 5        4-(4-Bromo-2-fluoroanilino)-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline hydrochloride (50mg) was suspended in methylene chloride (2ml) and was washed with saturated sodium hydrogen carbonate. The methylene chloride solution was dried ( $\text{MgSO}_4$ ) and the volatiles were removed by evaporation to give 4-(4-bromo-2-fluoroanilino)-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline (free base). The NMR of the free base  
10 so generated shows only one form as described below:

$^1\text{H}$  NMR Spectrum: ( $\text{DMSO-d}_6$ ) 1.3-1.45 (m, 2H) ; 1.76 (d, 2H) ; 1.7-1.9(m, 1H) ; 1.9 (t, 2H) ; 2.19 (s, 3H) ; 2.8 (d, 2H) ; 3.95 (s, 3H) ; 4.02 (d, 2H) ; 7.2 (s, 1H) ; 7.48 (d, 1H) ; 7.55 (t, 1H) ; 7.68 (dd, 1H) ; 7.8 (s, 1H) ; 8.38 (s, 1H) ; 9.55(br s, 1H)

- For another NMR reading, some  $\text{CF}_3\text{COOD}$  was added into the NMR DMSO solution  
15 of the 4-(4-bromo-2-fluoroanilino)-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline (free base) described above and the NMR spectrum was recorded again. The spectrum of the protonated form of the 4-(4-bromo-2-fluoroanilino)-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline trifluoroacetate salt so obtained shows the presence of two forms A and B in a ratio A:B of approximately 9:1.

- 20  $^1\text{H}$  NMR Spectrum: ( $\text{DMSO-d}_6$ ;  $\text{CF}_3\text{COOD}$ ) 1.5-1.7 (m, form A 2H); 1.93 (br s, form B 4H); 2.0-2.1 (d, form A 2H); 2.17 (br s, form A 1H); 2.35 (br s, form B 1H); 2.71 (s, form A 3H); 2.73 (s, form B 3H); 2.97-3.09 (t, form A 2H); 3.23 (br s, form B 2H); 3.34 (br s, form B 2H); 3.47-3.57 (d, form A 2H); 4.02 (s, 3H); 4.15 (d, form A 2H); 4.30 (d, form B 2H); 7.2 (s, 1H); 7.3-7.5 (m, 2H); 7.6 (d, 1H); 7.9 (s, 1H); 8.7 (s, 1H)

- 25        The starting material was prepared as follows:

- 1-(*tert*-Butoxycarbonyl)-4-(4-methylphenylsulphonyloxymethyl)piperidine (40g, 0.11mol), (prepared as described for the starting material in process (a) above), was added to a suspension of ethyl 4-hydroxy-3-methoxybenzoate (19.6g, 0.1mol) and potassium carbonate (28g, 0.2mol) in dry DMF (200ml). After stirring at 95°C for 2.5 hours, the mixture was  
30 cooled to ambient temperature and partitioned between water and ethyl acetate/ether. The organic layer was washed with water, brine, dried ( $\text{MgSO}_4$ ) and evaporated. The resulting oil was crystallised from petroleum ether and the suspension was stored overnight at 5°C. The

solid was collected by filtration, washed with petroleum ether and dried under vacuum to give ethyl 4-(1-(*tert*-butoxycarbonyl)piperidin-4-ylmethoxy)-3-methoxybenzoate (35g, 89%).

m.p. 81-83°C

MS (ESI): 416 [MNa]<sup>+</sup>

5 <sup>1</sup>H NMR Spectrum: (CDCl<sub>3</sub>) 1.2-1.35(m, 2H); 1.4(t, 3H); 1.48(s, 9H); 1.8-1.9(d, 2H); 2.0-2.15(m, 2H); 2.75(t, 2H); 3.9(d, 2H); 3.95(s, 3H); 4.05-4.25(br s, 2H); 4.35(q, 2H); 6.85(d, 1H); 7.55(s, 1H); 7.65(d, 1H)

Elemental analysis: Found C 63.4 H 8.0 N 3.5

C<sub>21</sub>H<sub>31</sub>NO<sub>6</sub> 0.3H<sub>2</sub>O Requires C 63.2 H 8.0 N 3.5%

10 Formaldehyde (12M, 37% in water, 35ml, 420mmol) was added to a solution of ethyl 4-(1-(*tert*-butoxycarbonyl)piperidin-4-ylmethoxy)-3-methoxybenzoate (35g, 89mmol) in formic acid (35ml). After stirring at 95°C for 3 hours, the volatiles were removed by evaporation. The residue was dissolved in methylene chloride and 3M hydrogen chloride in ether (40ml, 120mmol) was added. After dilution with ether, the mixture was triturated until a  
15 solid was formed. The solid was collected by filtration, washed with ether and dried under vacuum overnight at 50°C to give ethyl 3-methoxy-4-(1-methylpiperidin-4-ylmethoxy)benzoate (30.6g, quant.).

MS (ESI): 308 [MH]<sup>+</sup>

<sup>1</sup>H NMR Spectrum: (DMSO-d<sub>6</sub>) 1.29(t, 3H); 1.5-1.7(m, 2H); 1.95(d, 2H); 2.0-2.15(br s, 1H);  
20 2.72(s, 3H); 2.9-3.1(m, 2H); 3.35-3.5(br s, 2H); 3.85(s, 3H); 3.9-4.05(br s, 2H); 4.3(q, 2H); 7.1(d, 1H); 7.48(s, 1H); 7.6(d, 1H)

A solution of ethyl 3-methoxy-4-(1-methylpiperidin-4-ylmethoxy)benzoate (30.6g, 89mmol) in methylene chloride (75ml) was cooled to 0-5°C. TFA (37.5ml) was added followed by the dropwise addition over 15 minutes of a solution of fuming 24N nitric acid  
25 (7.42ml, 178mmol) in methylene chloride (15ml). After completion of the addition, the solution was allowed to warm up and stirred at ambient temperature for 2 hours. The volatiles were removed under vacuum and the residue was dissolved in methylene chloride (50ml). The solution was cooled to 0-5°C and ether was added. The precipitate was collected by filtration, and dried under vacuum at 50°C. The solid was dissolved in methylene chloride (500ml) and  
30 3M hydrogen chloride in ether (30ml) was added followed by ether (500ml). The solid was collected by filtration and dried under vacuum at 50°C to give ethyl 3-methoxy-4-(1-methylpiperidin-4-ylmethoxy)-6-nitrobenzoate (28.4g, 82%).

MS (ESI): 353 [MH]<sup>+</sup>

<sup>1</sup>H NMR Spectrum: (DMSO-d<sub>6</sub>) 1.3(t, 3H); 1.45-1.65(m, 2H); 1.75-2.1(m, 3H); 2.75(s, 3H); 2.9-3.05(m, 2H); 3.4-3.5(d, 2H); 3.95(s, 3H); 4.05(d, 2H); 4.3(q, 2H); 7.32(s, 1H); 7.66(s, 1H)

- 5 A suspension of ethyl 3-methoxy-4-(1-methylpiperidin-4-ylmethoxy)-6-nitrobenzoate (3.89g, 10mmol) in methanol (80ml) containing 10% platinum on activated carbon (50% wet) (389mg) was hydrogenated at 1.8 atmospheres pressure until uptake of hydrogen ceased. The mixture was filtered and the filtrate was evaporated. The residue was dissolved in water (30ml) and adjusted to pH10 with a saturated solution of sodium hydrogen carbonate. The
- 10 mixture was diluted with ethyl acetate/ether (1/1) and the organic layer was separated. The aqueous layer was further extracted with ethyl acetate/ether and the organic layers were combined. The organic layers were washed with water, brine, dried (MgSO<sub>4</sub>), filtered and evaporated. The resulting solid was triturated in a mixture of ether/petroleum ether, filtered, washed with petroleum ether and dried under vacuum at 60°C to give ethyl 6-amino-3-
- 15 methoxy-4-(1-methylpiperidin-4-ylmethoxy)benzoate (2.58g, 80%).

m.p. 111-112°C

MS (ESI): 323 [MH]<sup>+</sup>

<sup>1</sup>H NMR Spectrum: (CDCl<sub>3</sub>) 1.35(t, 3H); 1.4-1.5(m, 2H); 1.85(m, 3H); 1.95(t, 2H); 2.29(s, 3H); 2.9(d, 2H); 3.8(s, 3H); 3.85(d, 2H); 4.3(q, 2H); 5.55(br s, 2H); 6.13(s, 1H); 7.33(s, 1H)

- 20 Elemental analysis: Found C 62.8 H 8.5 N 8.3  
C<sub>17</sub>H<sub>26</sub>N<sub>2</sub>O<sub>4</sub> 0.2H<sub>2</sub>O Requires C 62.6 H 8.2 N 8.6%

- A solution of ethyl 6-amino-3-methoxy-4-(1-methylpiperidin-4-ylmethoxy)benzoate (16.1g, 50mmol) in 2-methoxyethanol (160ml) containing formamidine acetate (5.2g, 50mmol) was heated at 115°C for 2 hours. Formamidine acetate (10.4g, 100mmol) was added in
- 25 portions every 30 minutes over 4 hours. Heating was prolonged for 30 minutes after the last addition. After cooling, the volatiles were removed under vacuum. The solid was dissolved in ethanol (100ml) and methylene chloride (50ml). The precipitate was removed by filtration and the filtrate was concentrated to a final volume of 100ml. The suspension was cooled to 5°C and the solid was collected by filtration, washed with cold ethanol followed by ether and dried
- 30 under vacuum overnight at 60°C to give 6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)-3,4-dihydroquinazolin-4-one (12.7g, 70%).

MS (ESI): 304 [MH]<sup>+</sup>

<sup>1</sup>H NMR Spectrum: (DMSO-d<sub>6</sub>) 1.25-1.4(m, 2H); 1.75(d, 2H); 1.9(t, 1H); 1.9(s, 3H); 2.16(s, 2H); 2.8(d, 2H); 3.9(s, 3H); 4.0(d, 2H); 7.11(s, 1H); 7.44(s, 1H); 7.97(s, 1H)

A solution of 6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)-3,4-dihydroquinazolin-4-one (2.8g, 9.24mmol) in thionyl chloride (28ml) containing DMF (280μl) was heated at reflux  
5 at 85°C for 1 hour. After cooling, the volatiles were removed by evaporation. The precipitate was triturated with ether, filtered, washed with ether and dried under vacuum. The solid was dissolved in methylene chloride and saturated aqueous sodium hydrogen carbonate was added. The organic layer was separated, washed with water, brine, dried (MgSO<sub>4</sub>) and evaporated to give 4-chloro-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline (2.9g, 98%).

10 MS (ESI): 322 [MH]<sup>+</sup>

<sup>1</sup>H NMR Spectrum: (DMSO-d<sub>6</sub>) 1.3-1.5(m, 2H); 1.75-1.9(m, 3H); 2.0(t, 1H); 2.25(s, 3H); 2.85(d, 2H); 4.02(s, 3H); 4.12(d, 2H); 7.41(s, 1H); 7.46(s, 1H); 8.9(s, 1H)

Alternatively, the 6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)-3,4-dihydroquinazolin-4-one can be prepared as follows:

15 Sodium hydride (1.44g of a 60% suspension in mineral oil, 36mmol) was added in portions over 20 minutes to a solution of 7-benzyloxy-6-methoxy-3,4-dihydroquinazolin-4-one (8.46g, 30mmol), (prepared, for example, as described in WO 97/22596, Example 1), in DMF (70ml) and the mixture was stirred for 1.5 hours. Chloromethyl pivalate (5.65g, 37.5mmol) was added in portions and the mixture stirred for 2 hours at ambient temperature. The mixture  
20 was diluted with ethyl acetate (100ml) and poured onto ice/water (400ml) and 2N hydrochloric acid (4ml). The organic layer was separated and the aqueous layer extracted with ethyl acetate, the combined extracts were washed with brine, dried (MgSO<sub>4</sub>) and the solvent removed by evaporation. The residue was triturated with a mixture of ether and petroleum ether, the solid was collected by filtration and dried under vacuum to give 7-benzyloxy-6-methoxy-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one (10g, 84%).  
25

<sup>1</sup>H NMR Spectrum: (DMSO-d<sub>6</sub>) 1.11(s, 9H); 3.89(s, 3H); 5.3(s, 2H); 5.9(s, 2H); 7.27(s, 1H); 7.35(m, 1H); 7.47(t, 2H); 7.49(d, 2H); 7.51(s, 1H); 8.34(s, 1H)

A mixture of 7-benzyloxy-6-methoxy-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one (7g, 17.7mmol) and 10% palladium-on-charcoal catalyst (700mg) in ethyl acetate (250ml),  
30 DMF (50ml), methanol (50ml) and acetic acid (0.7ml) was stirred under hydrogen at atmospheric pressure for 40 minutes. The catalyst was removed by filtration and the solvent removed from the filtrate by evaporation. The residue was triturated with ether, collected by

filtration and dried under vacuum to give 7-hydroxy-6-methoxy-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one (4.36g, 80%).

<sup>1</sup>H NMR Spectrum: (DMSO-d<sub>6</sub>) 1.1(s, 9H); 3.89(s, 3H); 5.89(s, 2H); 7.0(s, 1H); 7.48(s, 1H); 8.5(s, 1H)

- 5 Triphenylphosphine (1.7g, 6.5mmol) was added under nitrogen to a suspension of 7-hydroxy-6-methoxy-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one (1.53g, 5mmol) in methylene chloride (20ml), followed by the addition of 1-(*tert*-butoxycarbonyl)-4-(hydroxymethyl)piperidine (1.29g, 6mmol), (prepared as described for the starting material in process (a) above), and by a solution of diethyl azodicarboxylate (1.13g, 6.5mmol) in
- 10 methylene chloride (5ml). After stirring for 30 minutes at ambient temperature, the reaction mixture was poured onto a column of silica and was eluted with ethyl acetate/petroleum ether (1/1 followed by 6/5, 6/4 and 7/3). Evaporation of the fractions containing the expected product led to an oil that crystallised following trituration with pentane. The solid was collected by filtration and dried under vacuum to give 7-(1-(*tert*-butoxycarbonyl)piperidin-4-
- 15 ylmethoxy)-6-methoxy-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one (232g, 92%).

MS - ESI: 526 [MNa]<sup>+</sup>

<sup>1</sup>H NMR Spectrum: (CDCl<sub>3</sub>) 1.20 (s, 9H), 1.2-1.35 (m, 2H), 1.43 (s, 9H), 1.87 (d, 2H), 2.05-2.2 (m, 1H), 2.75 (t, 2H), 3.96 (d, 2H), 3.97 (s, 3H), 4.1-4.25 (br s, 2H), 5.95 (s, 2H), 7.07 (s, 1H), 7.63 (s, 1H), 8.17 (s, 1H)

- |    |   |          |        |       |        |
|----|---|----------|--------|-------|--------|
| 20 | Elemental analysis:   | Found    | C 61.8 | H 7.5 | N 8.3  |
|    | C <sub>26</sub> H <sub>37</sub> N <sub>3</sub> O <sub>7</sub> | Requires | C 62.0 | H 7.4 | N 8.3% |

- A solution of 7-(1-(*tert*-butoxycarbonyl)piperidin-4-ylmethoxy)-6-methoxy-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one (2.32g, 4.6mmol) in methylene chloride (23ml) containing TFA (5ml) was stirred at ambient temperature for 1 hour. The volatiles
- 25 were removed under vacuum. The residue was partitioned between ethyl acetate and sodium hydrogen carbonate. The organic solvent was removed under vacuum and the residue was filtered. The precipitate was washed with water, and dried under vacuum. The solid was azeotroped with toluene and dried under vacuum to give 6-methoxy-7-(piperidin-4-ylmethoxy)-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one (1.7g, 92%).

- 30 MS - ESI: 404 [MH]<sup>+</sup>

<sup>1</sup>H NMR Spectrum: (DMSO-d<sub>6</sub>; CF<sub>3</sub>COOD) 1.15 (s, 9H), 1.45-1.6 (m, 2H), 1.95 (d, 2H), 2.1-2.25 (m, 1H), 2.95 (t, 2H), 3.35 (d, 2H), 3.95 (s, 3H), 4.1 (d, 2H), 5.95 (s, 2H), 7.23 (s, 1H), 7.54 (s, 1H), 8.45 (s, 1H)

A 37% aqueous solution of formaldehyde (501μl, 6mmol) followed by sodium cyanoborohydride (228mg, 3.6mmol) were added in portions to a solution of 6-methoxy-7-(piperidin-4-ylmethoxy)-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one (1.21g, 3mmol) in a mixture of THF/methanol (10ml/10ml). After stirring for 30 minutes at ambient temperature, the organic solvents were removed under vacuum and the residue was partitioned between methylene chloride and water. The organic layer was separated, washed with water and brine, dried (MgSO<sub>4</sub>) and the volatiles were removed by evaporation. The residue was triturated with ether and the resulting solid was collected by filtration, washed with ether and dried under vacuum to give 6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one (1.02g, 82%).

MS - ESI: 418 [MH]<sup>+</sup>

<sup>1</sup>H NMR Spectrum: (CDCl<sub>3</sub>) 1.19 (s, 9H), 1.4-1.55 (m, 2H), 1.9 (d, 2H), 2.0 (t, 2H), 1.85-2.1 (m, 1H), 2.3 (s, 3H), 2.92 (d, 2H), 3.96 (s, 3H), 3.99 (d, 2H), 5.94 (s, 2H), 7.08 (s, 1H), 7.63 (s, 1H), 8.17 (s, 1H)

A saturated solution of ammonia in methanol (14ml) was added to a solution of 6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one (1.38g, 3.3mmol) in methanol (5ml). After stirring for 20 hours at ambient temperature, the suspension was diluted with methylene chloride (10ml). The solution was filtered. The filtrate was evaporated under vacuum and the residue was triturated with ether, collected by filtration, washed with ether and dried under vacuum to give 6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)-3,4-dihydroquinazolin-4-one (910mg, 83%).

MS - ESI: 304 [MH]<sup>+</sup>

<sup>1</sup>H NMR Spectrum: (DMSO-d<sub>6</sub>) 1.3-1.45 (m, 2H), 1.75 (d, 2H), 1.7-1.85 (m, 1H), 1.9 (t, 2H), 2.2 (s, 3H), 2.8 (d, 2H), 3.9 (s, 3H), 4.0 (d, 2H), 7.13 (s, 1H), 7.45 (s, 1H), 7.99 (s, 1H)

The following tests were used to demonstrate the activity of ZD6474 in combination with ionising radiation.

#### Calu-6 Xenograft Model

Calu-6 (lung carcinoma) cells were obtained from the American Type Culture Collection (Manassas, VA). All cell culture reagents, where not specified, were obtained from

Life Technologies, Paisley, UK. Cells were maintained as exponentially growing monolayers in Eagle's Minimal Essential Medium (EMEM) containing 10% FCS (Labtech International, Ringmer, UK), 2mM L-glutamine (Sigma Chemical Co., Poole, UK), 1% sodium pyruvate (100mM) and 1% non-essential amino acids. Cells were periodically screened for the presence of microplasma in culture, and analysed for 15 types of virus in a mouse antibody production test (AstraZeneca Central Toxicology Laboratories, Alderley Park, UK) prior to routine use *in vivo*.

Calu-6 cells ( $2 \times 10^7$  cells/ml) were prepared for implantation in a mixture of 50% (v/v) matrigel (Fred Baker, Liverpool, UK) in serum free Roswell Park Memorial Institute (RPMI)-1640 media. Tumour xenografts were established by subcutaneously injecting 0.1ml of the cell suspension (i.e.  $2 \times 10^6$  cells/mouse) into female Alderley Park nude mice (nu/nu genotype; 8-10 weeks of age). Once a palpable tumour was evident, tumour volume was assessed daily by calliper measurement and calculated using the formula, length x width x height.

Mice were randomised into groups of eight, prior to treatment, when tumours measured 225-315 mm<sup>3</sup>. Ionising radiation, where given, was administered at a dose rate of 2Gy per min to unanaesthetised mice restrained in polyvinyl jigs with lead shielding and a cut away section to allow local irradiation of the tumour by the unilateral beam (Pantac X-ray set). Jigs were turned through 180° halfway through the radiation exposure time to provide a uniform dosing. Radiation was administered either as a single dose (5Gy on day 1) or by multiple daily dosing (2Gy/day on days 1-3). Thirty minutes after the last dose of radiation, ZD6474 (25 mg/kg), or vehicle, was administered by oral gavage (0.1ml/10g body weight) and then once-daily thereafter for a further 13 days (i.e. 14 days of oral treatment in total). ZD6474 was prepared as a suspension in 1% polysorbate 80 (i.e. a 1% (v/v) solution of polyoxyethylene (20) sorbitan mono-oleate in deionised water). Mice were humanely killed when the relative volume of their tumour reached four times that at the initiation of therapy (RTV<sub>4</sub>). A two-tailed two-sample *t*-test was used to evaluate the significance of the results obtained.

**Table 1 - RTV<sub>4</sub> in Days**

<b>Radiation Treatment</b>	<b>Drug Treatment (for 14 days post-irradiation)</b>	<b>RTV<sub>4</sub> (days)</b>	<b>SE</b>
None	ZD6474 Vehicle	8.8	0.7
5 Gy	ZD6474 Vehicle	20.0	1.5
3 x 2Gy	ZD6474 Vehicle	23.1	1.3
None	ZD6474 (25 mg/kg/day)	12.1	0.4
5 Gy	ZD6474 (25 mg/kg/day)	25.5	0.5
3 x 2Gy	ZD6474 (25 mg/kg/day)	28.1	0.7

The data are shown graphically in Figure 1 and Figure 2.

The data indicate that in each case (5Gy or 3 x 2Gy experiments) the combination of radiation plus ZD6474 provided a better therapeutic effect than either therapy alone.

<b>RTV<sub>4</sub> Comparison</b>	<b>P value*</b>
(5Gy + ZD6474) Vs. (5Gy + vehicle)	0.006
(5Gy + ZD6474) Vs. (ZD6474)	P<0.001
(3 x 2Gy + ZD6474) Vs. (3 x 2Gy + vehicle)	0.007
(3 x 2Gy + ZD6474) Vs. (ZD6474)	P<0.001

\* P value by two-sample t-test (assuming unequal variance)

10 In an analogous experiment using the Calu-6 xenograft model described hereinbefore different schedules were investigated.

Mice bearing Calu-6 tumours (220–300 mm<sup>3</sup>) were randomized into groups of eight, to receive either ZD6474 (50 mg/kg p.o. once daily) or vehicle only (1% polysorbate in deionized water) for the duration of the experiment. ZD6474, or vehicle, was also administered with or



without radiotherapy (3 x 2 Gy at 24-hour intervals during the first 3 days of treatment). Where mice received 50 mg/kg ZD6474 plus radiation therapy, two treatment schedules were examined:

- a) Concurrent combination treatment: ZD6474 dosing given 2 hours prior to the first dose of radiation; and
- b) Sequential combination treatment: ZD6474 dosing given 30 minutes after the last dose of radiotherapy.

An additional group of mice bearing Calu-6 xenografts were treated with vehicle and 5 x 2 Gy of radiotherapy at 24-hour intervals.

- 10 Treatment efficacy was assessed by measuring the time for tumours to quadruple in volume (RTV<sub>4</sub>) from their pretreatment size and calculating the relative growth delay (i.e. comparing RTV<sub>4</sub> values from individual treated groups, with that of the control).

**Table 2 – RTV<sub>4</sub> and Tumour growth delay in days**

Treatment (n=8 per group)	RTV <sub>4</sub> (days ± SE)	Growth delay (days ± SE)
Vehicle	8 ± 0.5	NA
50 mg/kg ZD6474	17 ± 1.0	9 ± 1.1
3 x 2 Gy plus vehicle	25 ± 1.7	17 ± 1.8
3 x 2 Gy plus 50 mg/kg ZD6474 (sequential)	44 ± 0.9	36 ± 1.0
3 x 2 Gy plus 50 mg/kg ZD6474 (concurrent)	30 ± 1.0	22 ± 1.1
5 x 2 Gy plus vehicle	46 ± 4.0*	38 ± 4.0

- 15 \* based upon n = 7; one tumour/group did not achieve RTV<sub>4</sub> within 100 days post-treatment

The data are shown graphically in Figure 3.

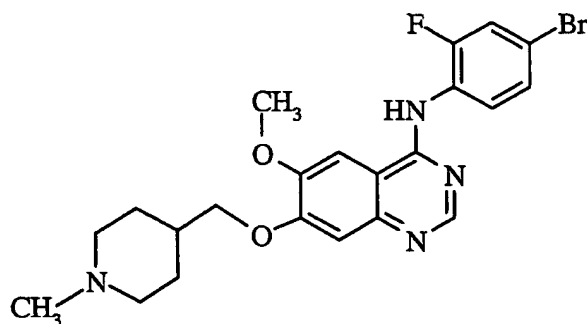
- 20 The data show that 50 mg/kg dose of ZD6474 combined with 3 x 2 Gy radiation treatment gave a growth delay that was significantly greater than that of either single treatment alone.

Sequential combination treatment with radiation and 50 mg/kg ZD6474 inhibited tumour growth significantly more than when the same agents were combined concurrently (growth delays of  $36 \pm 1.0$  days and  $22 \pm 1.1$  days respectively).

The antitumour effect produced by sequential combination treatment with 3 x 2 Gy radiation and 50 mg/kg ZD6474 was greater than the sum of the growth delays induced by the individual therapies, and comparable to treatment with 5 x 2 Gy of radiation alone.

**CLAIMS**

1. A method for the production of an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal such as a human, which comprises administering to  
5 said animal an effective amount of 4-(4-bromo-2-fluoroanilino)-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline, also known as ZD6474:



10

ZD6474

or a pharmaceutically acceptable salt thereof, before, after or simultaneously with an effective amount of ionising radiation.

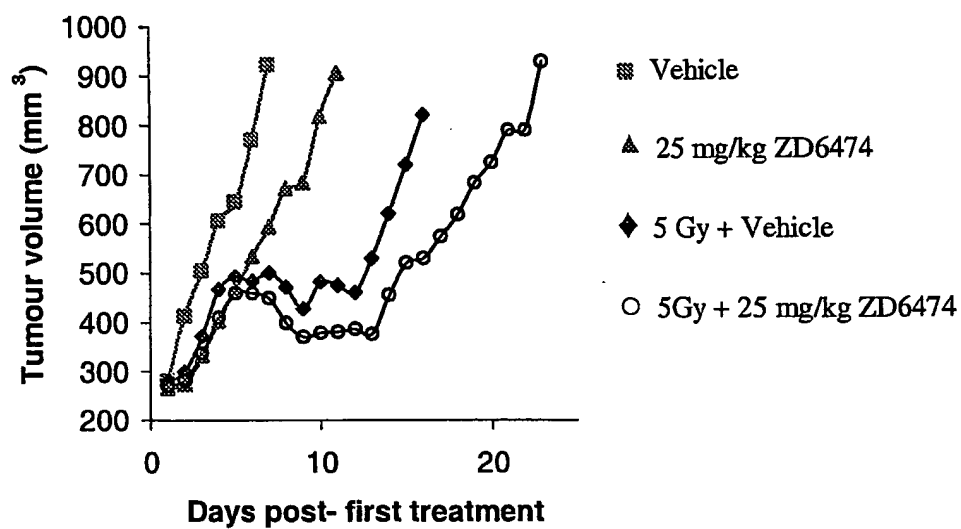
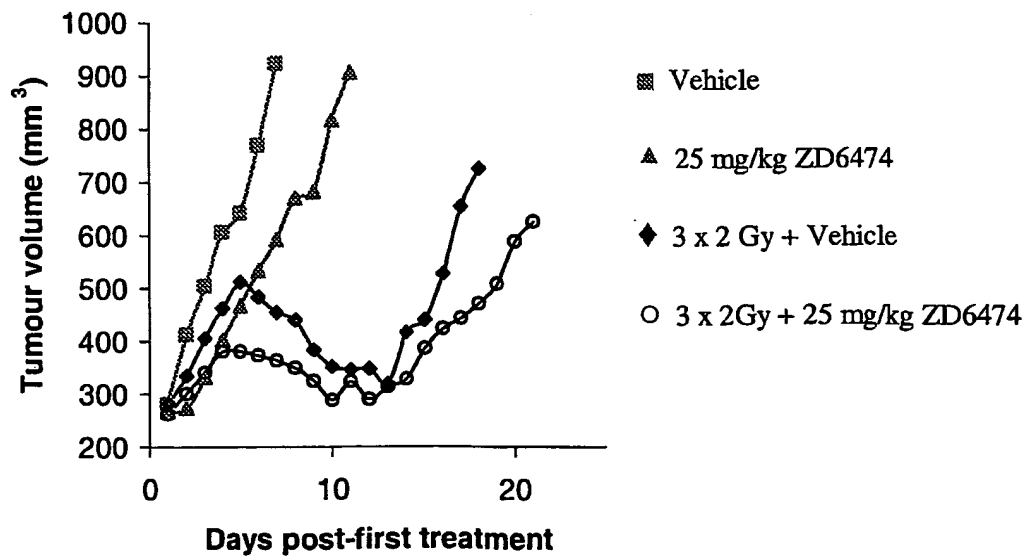
2. A method for the treatment of a cancer in a warm-blooded animal such as a human,  
15 which comprises administering to said animal an effective amount of ZD6474 or a pharmaceutically acceptable salt thereof, before, after or simultaneously with an effective amount of ionising radiation.

3. A method for the treatment of a cancer involving a solid tumour in a warm-blooded  
20 animal such as a human, which comprises administering to said animal an effective amount of ZD6474 or a pharmaceutically acceptable salt thereof, before, after or simultaneously with an effective amount of ionising radiation.

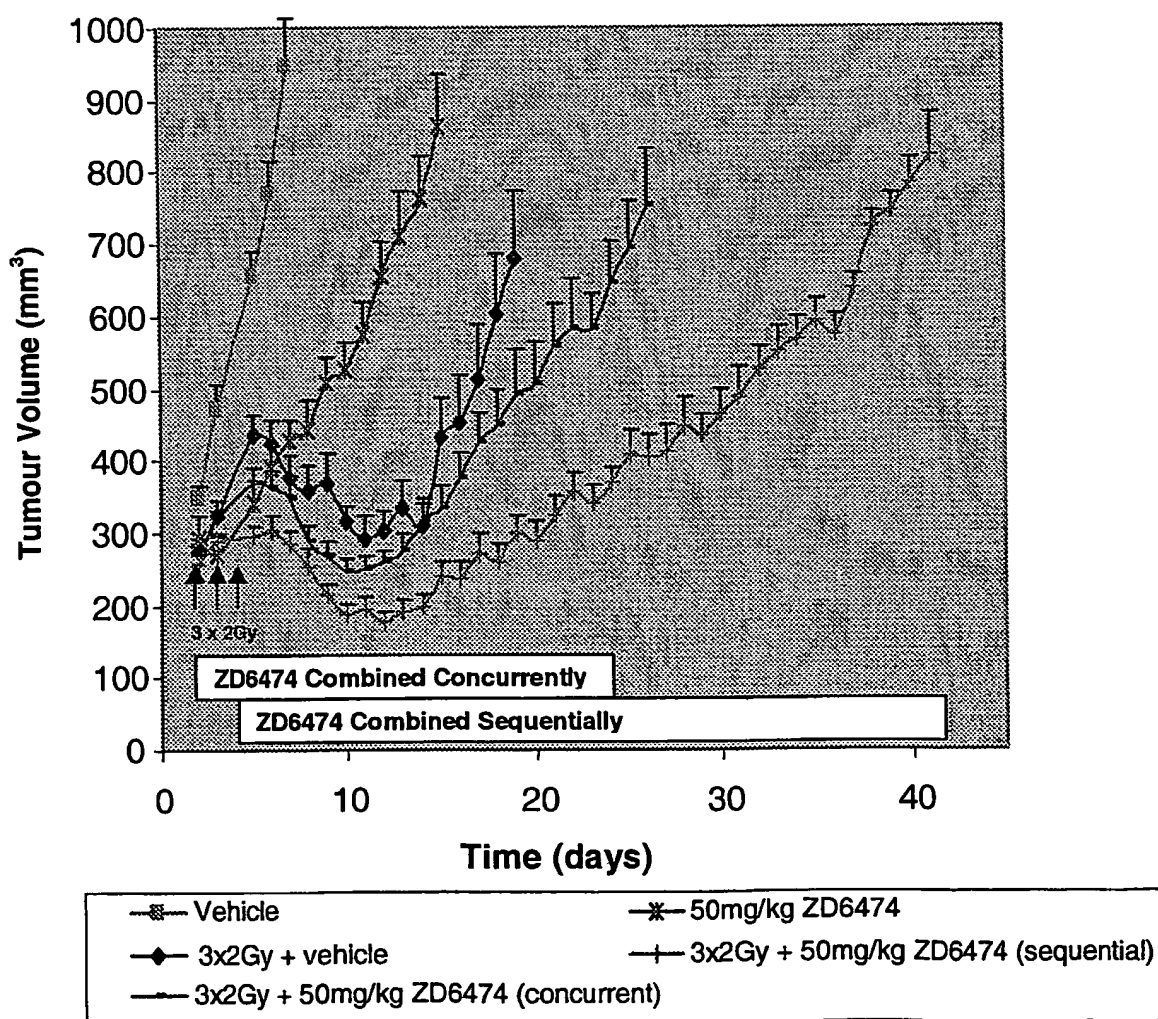
4. Use of ZD6474 or a pharmaceutically acceptable salt thereof in the manufacture of a  
25 medicament for use in the production of an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal such as a human which is being treated with ionising radiation.

5. Use of ZD6474 or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in the production of an anti-cancer effect in a warm-blooded animal such as a human which is being treated with ionising radiation.

- 5        6. Use of ZD6474 or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in the production of an anti-tumour effect in a warm-blooded animal such as a human which is being treated with ionising radiation.

**Figure 1****Figure 2**

**Figure 3.** Sequential versus concurrent ZD6474 treatment scheduling influences the relative enhancement in radiotherapeutic response seen. Mean values for tumour size ( $\pm$  SE) in each treatment group are given. Concurrent schedule: continuous ZD6474 (50 mg/kg/day; day 1 onwards) with the first dose administered 2 hours prior to the first dose of radiotherapy (2 Gy/day, days 1–3). Sequential schedule: continuous ZD6474 (50 mg/kg/day; day 3 onwards) with the first dose administered 0.5 hour after the last dose of radiotherapy (2 Gy/day, days 1–3).



**Figure 3**

# INTERNATIONAL SEARCH REPORT

PC/GB 03/03388

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/517 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BIOSIS, EMBASE, PASCAL

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>WO 01 32651 A (HENNEQUIN LAURENT FRANCOIS AND ;THOMAS ANDREW PETER (GB); ASTRAZEN)  10 May 2001 (2001-05-10)  cited in the application  page 1, line 3 - line 8  claims 8,12  page 28, line 11 - line 17  page 26, line 22 - line 30  ---</p> <p style="text-align: center;">-/--</p>	1-6

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- \*G\* document member of the same patent family

Date of the actual completion of the international search

2 October 2003

Date of mailing of the international search report

28/10/2003

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## INTERNATIONAL SEARCH REPORT

PC 7 GB 03/03388

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>HESS C ET AL: "EFFECT OF VEGF RECEPTOR INHIBITOR PTK787/ZK222548 COMBINED WITH IONIZING RADIATION ON ENDOTHELIAL CELLS AND TUMOUR GROWTH" BRITISH JOURNAL OF CANCER, LONDON, GB, vol. 85, no. 12, 2001, pages 2010-2016, XP008018114 ISSN: 0007-0920 page 2010, right-hand column, paragraphs 2,3 -page 2011, left-hand column, paragraph 1 page 2014, right-hand column, paragraph 2 -page 2015, left-hand column, paragraphs 1,2</p>	1-6
Y	<p>----- GORSKI, H.; BECKETT, M.A.; JAKOWIAK, N.T.; CALVIN, D.P.; MAUCERI, H.J.; SALLOUM, R.M.; SEETHARAM, S.; KOONS, A.; HARI, D.M.: " Blockade of the Vascular Endothelial Growth Factor Stress Response Increases the Antitumor Effects of Ionizing Radiation" CANCER RESEARCH, vol. 59, 15 July 1999 (1999-07-15), pages 3374-3378, XP002256383 page 3377, right-hand column, line 18 - line 25 page 3378, right-hand column, line 13 - line 21 -----</p>	1-6



# INTERNATIONAL SEARCH REPORT

PCT/GB 03/03388

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0132651	A	10-05-2001	
		AU 1288601 A	14-05-2001
		BG 106659 A	31-03-2003
		BR 0015203 A	16-07-2002
		CA 2389767 A1	10-05-2001
		CN 1387527 T	25-12-2002
		CZ 20021526 A3	17-07-2002
		EE 200200237 A	16-06-2003
		EP 1244647 A1	02-10-2002
		WO 0132651 A1	10-05-2001
		HU 0203453 A2	28-05-2003
		JP 2003513089 T	08-04-2003
		NO 20022139 A	03-05-2002
		SK 6122002 A3	09-01-2003